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10/005,469	11/07/2001	Vadim Bichko	0342/1H395US1	7244

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DARBY & DARBY P.C.
805 Third Avenue
New York, NY 10022

EXAMINER
LI, BAO Q

ART UNIT	PAPER NUMBER
1648	12

DATE MAILED: 06/03/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/005,469	BICHKO, VADIM	
	Examiner	Art Unit	
	Bao Qun Li	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 February 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) *4 and 6-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3 and 5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☐ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3&9* .
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other:

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I, claims 1-3 and 5 in the scope of double stranded DNA in Paper No. 11 is acknowledged. The traversal is on the ground(s) that search of the subject matter of the claims of Group I would necessarily include a search of the subject matter of the claims of Group II and Group III as they all involve recombinant HCV nucleic acid sequences, therefore, it would not present an undue burden on the examiner. This is not found persuasive because Applicant does not claim the product of the Group II is the product of group I. The search of the nucleic acid construct of group I as it was presented in the claims does not relate to any particular nuclei acid sequence search of group II. Furthermore, the product of Group III is a cell, which does not have any structurally and functionally similarity to the nucleic acid molecule. It has different patentable weight and constitutes a distinct invention. Therefore, groups II and III are not rejoined with Group I.

2. Regarding to the further election of different kinds of nucleic acid molecules, during the examination, the restriction has been withdraw. The claims have been examined on the full scope covering all kinds of nucleic acid molecules as listed in claim 5.

3. Claims 1-3 and 5 are considered before examiner.

4. Applicant is reminded to cancel the claims 4 and 6-22 drawn to the non-elected groups.

Claim Rejections - 35 USC § 112

5. Claims 1-3 and 5 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated novel nucleic acid molecule encoding a replication competent recombinant HCV genome I377/NS3-3'UTR having some particular mutations after long time cell culture that enable it replicate efficiently without significantly reducing the cell growth rate for more than 10 fold, does not reasonably provide enablement for having a nucleic acid molecule encoding any full or part of a HCV genome that is able to replicate efficiently when it is transfected into a susceptible cell line without significantly reducing the growth rate of a susceptible cell line by more than 10 fold. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

6. The test of scope of the enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the application coupled with information known in the art would undue experimentation (See United States v. Theketronic Inc., 8USPQ2d 1217 (fed Cir. 1988). Whether undue experimentation is required is not based upon a single factor but rather a conclusion reached by weighting many factors. Theses factors were outlined in Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and gain in re Wands, 8USPQ2d 1400 (Fed. Cir. 1988). These factors include the following:

1) & 2) State of art and unpredictability of the field.

The technique of constructing a nucleic acid construct comprising full or part of hepatitis C virus genome, which is used for transfecting susceptible cell line, is known in the art. However, it is very unpredictable that every construct will be able to become replication efficient without reducing the host cell growth for more than 10 fold when it is transected into a cell line because it is unpredictable that every HCV genome or any part of HCV genome can be used as a replication replicon for transfecting a cell without significantly reducing the cell grow. This unpredictable is manifested by the following characteristics of the HCV genome:

(1) HCV genome has high level of heterogeneity. The genetic quasispecies of HCV results from the rapid mutation during the HCV viral replication consistently as described by Bukh et al. (Siminars in liver disease 1995, Vol. 15, No. 1, pp. 41-63, see 13-128 in 1st col. of page 44). This is also demonstrated by Applicant's own work in that he use one cloned construct to transfect Huh-7 cell. Among 33 cloned cells, he is only able to isolated 5 clones meeting the claimed growth rate and each of them has different mutations. More importantly, different mutated HCV genomes behave differently as demonstrated by Yanagi et al. (Virology 1998, Vol. 244, pp. 161-172). They demonstrate that an in-vivo transfection of chimpanzees with transcriptions of a chimeric HCV cDNA result in different clones and only one clone became infectious due to its unique mutation than other two non-infectious clones;

(2) Due to the heterogeneity, transfection of some HCV RNA transcripts are more toxic than to the recipient cells as evidenced by Yoo et al. (J. Virol. 1995, Vol. 69, No. 1, p. 32-38) and Houghton et al. (US Patent No. 5/679,342A). They both teach that the transfection of the transcript of the replication HCV full-length genotype $_{R}HCV_{F}$ genome or its subgenomic $_{R}HCV_{S}$ cDNA into the Huh-7 cells significantly reduce the growth rate of the recipient cells for about

more than 10 fold (See Yoo et al. Fig. 1 and lines 4-11 on page 33 and Fig. 5 on page 36; Houghton et al. Fig. 4A and lines 13-26 on col. 25); and

(3). It is not every nucleic acid construct comprising any part of the HCV genome that will support replicate efficient as evidenced by Yanagi et al. (P.N.A.S. 1999, Vol. 96, pp. 2291-2295, see entire document). Yanagi et al. teach that the truncated HCV genomes lacking all or part of the 3'termal conserved region or the poly (U-C) region are unable to infect the chimpanzee (See abstract).

3) & 4) Number of working examples and Amount of guidance.

Applicant only teach that an isolated a nucleic acid molecule I377/NS3-3' comprising 5' and 3' NTR, and HCV non-structural protein NS3 to the 3' end with some particular mutations that is able to replicate efficiently without significantly influence the cell growth rate for more than 10 fold after long time cell culture.

However, Applicant does not teach that any isolated nucleic acid molecule encoding a full-length of a HCV genome or other partial HCV genome rather than from NS2 to 3' end is able be transfected into a susceptible cell, and replicates efficiently without cause the reduction of cell growth rate less than 10 fold. For example, HCV structural protein capsid C protein does not encode any HCV replication enzyme, it does not support the HCV replication.

Furthermore, Applicant does not teach which portion of the HCV polypeptide is able to form functional component of HCV viral particle. All non-structural proteins from NS2 to NS5B in the construct as used by Applicant are not the necessary component for forming the HCV virus particle because HCV particle is constituted by the HCV structural proteins: capsid protein or name core protein: C and envelope proteins: E1 and E2.

Moreover, Applicant does not teach other cell line rather than Huh-7 is susceptible for the said nucleic acid molecule transfection and replication. Because not every kind of cell line is susceptible for the replication of HCV as evidenced by Dash et al. (Am. J. Patho. 1997, Vol. 51, No. 2, pp. 363-373) and Bartenschahlager et al. (J. Gene. Virol. 2000, Vol. 81, pp. 1613-648). Dash et al. teach that transfection of full-length or nearly full-length of HCV RNA into the human hepatoma cell line HepG2 kills all cells after 50-60 days after transfection (See line 1-5 on 1st col. of page 368). Bartenschahlager et al. teach that some specific host cell factors in a few

cell lines may involves in the HCV replication; therefore, they are only able to obtain the HCV transfected clones in Huh-7 cell line.

5). Scope of the claims.

The claims broad read on any or all isolated nucleic acid molecule comprising any full or part of HCV genome that is able to replicate efficiently when transfected into a susceptible cells without reducing the growth rate of the cells for more than 10 fold.

6) & 7). Nature of the invention & Level of skill in the art.

The nature of the invention involves a random isolation of a replication competent recombinant HCV clone by transfecting a cell line with a transcribe of a HCV cDNA, wherein the HCV is able to replicated without significantly influence the host cell growth for more than 10 fold. Basis upon the characteristic of HCV genome, this selection requires high technology and skill to perform a random search for a particular mutated HCV clone. Because the HCV genome mutation is unpredictable, it will result in an undue experimentation for a skilled artisan to practice successful the full scope of the claimed invention.

Given the above analysis of the factors, which the courts have determined, are critical in asserting whether a claimed invention is enabled, it must be considered that the skilled artisan would have to conduct undue and excessive experimentation in order to practice the claimed invention.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 1, 3 and 5 are rejected under 35 U.S.C. 102(b) as being anticipated by Lohmann et al. (Science July 1999, Vol. 285-pp. 110-113).

9. Lohmann et al. disclose that several nucleic acid constructs that are able to replicate efficiently when transfected into human hepatoma Huh-7 cell. The constructs encode subgenomic selectable replicon of HCV: I377/NS2-3' or I377/NS3-3' and I389/NS2-3' or

I389/NS3-3', in which the HCV genome orientated from the 5' to 3' comprise the 5' and 3' non-translated region (NTR), the 5' HCV IRES, the neo gene, the EMCV-IRES (E-I), the HCV sequence from NS2 or NS3 up to the authentic 3' end (See Fig. 1 on page 111), wherein the authentic 5' NRT is placed down stream of the T7 promoter (See lines 23-26 on the 1st col. of page 113). The neo gene is a heterologous gene operably associated with an expression control sequences of HCV IRES and upstream T7 promoter. The open reading frames of constructs comprising at least portion of the HCV polypeptide starting from the non-structural protein NS2 to the 3' end or starting from NS3 till the 3' end (See Fig. 1 on page 111). Lohmann et al. also teach that after transfection of the transcripts of said HCV replicons cDNA into human Huh-7 cell line, they isolated 9 replication competent recombinant HCV clones. Three of these clones are found to produce a high amount positive and negative strands of HCV RNA encoding same sequences inherently as described above (See lines 6-23 on 2nd col. of page 111 and Fig. 2 on page 111). Because the nucleic acid molecule recited in claims 1, 3 and 5 do not have any structurally difference as compared with the nucleic acid construct taught by Lohmann et al. and according to Applicant own disclosure that he use the same construct (I377/NS3-3'UTR) and cell line (Huh-7) that Lohmann et al. used (See lines 19 on page 34 through line 10 on page 35 of specification) for the transfection and isolation, the claims are anticipated by the prior art of Lohmann et al.

10. Regarding to the limitation of " without reducing the growth rate of said cell line by more than 10 fold", Office does not see this limitation make the claimed product any structural difference compared with the product disclosed by Lohmann et al. While Lohmann et al. teach that the transfection of the construct into Huh-7 cell line reduces the doubling time in their 3-5 weeks post transfection observation, they do not particularly teach that the reduction is so significant that it is more than 10 fold lower than the parental cell line. Moreover, according to Applicant own disclosure that he also found the isolated clones having same characteristic as that of Lohmann et al. about growing slower at the post transfection 3-5 weeks period (See lines 19 on page 34 through line 10 on page 35 of specification); however, when he prolonged the observation of the cloned cell lines after 6 weeks, the cloned cells started to grow to the same rate as that of parental cells (See lines 16-24 of specification). From this point, Office would like to comment that the claimed characteristics is a common phenomenon for any cell cloning or cell

colony assay because when cells are split at very low density, the cells grow in a very low rate and it takes long time to reach the log path growing. It is a common knowledge that the cell log path growth has to wait until the cell density reaching to a certain level. The time for reaching this point really depends on the initial cell density that you split in the culture dish. Moreover, this phenomenon is also related to the cells recovery after treatment of transfection. For example, if the transfection efficiency is lower, most untransfected cells are died, only very few or couple of single cell that get transfected survive. A single cell takes a long time to grow as a colony and you have to gently break up the clumpy of the cell colony and split them in order for them to continuous grow fast and well. Otherwise the colony of cells stops to grow or died due to a contact inhibition. Nevertheless, because Applicant used the same construct of Lohmann et al. for the transfection into the same kind of cell, this prolonged observation does not add any more structural difference and patentable weight compared with the construct disclosed by Lohmann et al. because a person in the art can say that if Lohmann et al. al. keep their cell culture longer enough, sooner or later they will observed same phenomena. Office believes that same structure of two molecules should inherently have same biological characteristic. Hence, the claimed invention is anticipated by Lohmann et al.

11. Regarding to the 102 inherency rejection, Applicant's attention is directed to **See In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977) [PTO can require an applicant to establish that a prior art product does not necessarily possess the characteristics of the claimed product when the prior art and claimed products are identical or substantially identical.] While "indirect comparisons, based on established scientific principles, can validly be applied to distinguish a claimed chemical process or product from that disclosed in the prior art," In re Best, 562 F.2d 1252, 1254, 195 USPQ 430, 432 (CCPA 1977), the comparisons must be scientifically valid. Patent owner's burden under the circumstances presented herein was described in In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433-434 (CCPA 1977) as follows:**

12. **Where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. . . . Whether the rejection is based on**

`inherency' under 35 U.S.C. § 102, on `prima facie obviousness' under 35 U.S.C. § 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products [footnote omitted].

13. Claims 1-3 and 5 are rejected under 35 U.S.C. 102(b) as being anticipated by Rice et al. (WO 98/39031A1).

14. Rice et al. disclose a genetically engineered hepatitis C virus (HCV) nucleic acid clone, which comprises from 5' to 3' a functional 5' non-translated region (NTR) with extreme 5'-terminal conserved sequence, a open reading frame (ORF) encoding at least a portion of an HCV polyprotein whose cleavage products from functional components of HCV virus particles and RNA replication machinery, and 3' NTR comprising an extreme 3'-terminal conserved sequence (Clam 1 and Fig. 4 and lines 22-28 on page 12). Nucleic acid is a DNA that encodes an expression for a replication-component HCV RNA replicon, which is a replication-component HCV RNA replicon (Claim5). The HCV nucleic acid further comprises a heterologous gene operably associated with an expression control sequence, wherein the heterologous gene is an antibiotic resistance gene or a reporter gene. The heterologus gene and the expression control sequence are all oriented on the positive-strand nucleic acid molecule (Claims 10 and 12). Rice et al. further claim that the HCV nucleic acid construct is selected from group consisting of a double stranded DNA, positive cDNA, positive-sense cDNA, or negative-sense cDNA (Claim 14). Rice et al. also teach that a method of producing such HCV virus particle comprises transfection of a host cell line with said HCV DNA (Claim 39), or transcript of said DNA into a human hepatocyte cell line (See EXAMPLE 5 on page 95-96).

15. Regarding to the limitation of "replication efficient and without reducing the growth of said cell line 10-fold", Rice teach that right after transfection, most cells died, but a G418 (inserted drug resistant gene for the positive transfection selection) population grew up over the course of a few months. Remarkably, HCV RNA appears to be still present in these cells at a copy of about 100 RNA molecules per cell (See lines 8-14 on page 96). This indicates that the characteristic of reducing the cell growth if exist, is only a temporary phenomena. Therefore, Office does not give this temporary phenomena any structural difference and patentable distinctness of the claimed nucleic acid molecule as compared with the nucleic acid clone

disclosed by Rice et al. since both of them have same structural characteristics. If two molecules have same structural characteristics, Office will consider these two molecules inherently having same biological characteristics or functions. Hence the claimed invention is anticipated by the prior art.

16. Regarding to the 102 inherency rejection, Applicant's attention is directed to **See In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977) [PTO can require an applicant to establish that a prior art product does not necessarily possess the characteristics of the claimed product when the prior art and claimed products are identical or substantially identical.] While "indirect comparisons, based on established scientific principles, can validly be applied to distinguish a claimed chemical process or product from that disclosed in the prior art," In re Best, 562 F.2d 1252, 1254, 195 USPQ 430, 432 (CCPA 1977), the comparisons must be scientifically valid. Patent owner's burden under the circumstances presented herein was described in In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433-434 (CCPA 1977) as follows:**

17. **Where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. . . . Whether the rejection is based on `inherency' under 35 U.S.C. § 102, on `prima facie obviousness' under 35 U.S.C. § 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products [footnote omitted].**

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bao Qun Li whose telephone number is 703-305-1695. The examiner can normally be reached on 7:00 to 4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 703-308-4027. The fax phone numbers for the

organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Bao Qun Li
May 30, 2003